The Present Invention

Many topical products contain chemicals or other components that can produce irritation when applied to skin of animal subjects. The possibility of irritation is higher for persons that otherwise have sensitive skin. While such irritants may impart desirable effects, it is preferable that the irritation produced by their application be minimized or eliminated. As such, the present invention is directed to improved compositions and methods for topical application to animal subjects, wherein the compositions comprise not only at least one irritant ingredient in an amount capable of inducing skin irritation in a subject, but also an anti-irritant amount of aqueous-soluble divalent calcium cation and at least one aqueous-ionizable counter-anionic species.

From a formulation standpoint, it is preferred that the cation component is incorporated by mixing an appropriate amount of a suitable salt form of the cation into a topical vehicle with other components. It is further preferred that the selected salt is sufficiently soluble in the topical vehicle so as to allow a consistent formulation having desired physical and topical application characteristics. Depending on the topical vehicle, the salt form of the cation may dissociate within the formulation and associate with any other anions also present in the formulation. Alternatively, the salt form of the cation may remain substantially associated within the formulation. It is also highly preferred that the salt(s) chosen be sufficiently aqueous-soluble such that, upon application to skin, the cation and any anion components can dissociate and be taken up into water-containing milieu of the skin.

In an exemplary embodiment, the present invention utilizes an anti-irritant amount of calcium cation accompanied (as in the form of a salt) by one or more ionizing anionic species in a topical vehicle. It is believed that pairing of the cation with one or more anionic species imparts a desired and previously unobtainable level of acidity or basicity to a formulated composition that effectively reduces skin irritation.

It is often desirable to maintain the pH of resulting formulations to a relatively acidic level, as for example in the case of hydroxy-acid or other acidic exfoliant products where the activity of the product to reduce wrinkles or bring about other beneficial effects may be reduced if the formulation is not relatively acidic. In one such particularly

preferred embodiment, the calcium cation component of the present invention is combined in a hydroxyl acid or other exfoliant preparation accompanied by one or more suitable anionic species such that the pH of the hydroxyl acid preparation is maintained in the range of pH 1-6, and more preferably in the range of pH 2-4.

Examples of potentially suitable anionic species include a variety of mono-, di- and trivalent inorganic and organic anions. Examples of potentially suitable inorganic anions include nitrate, sulfate, halogens (particularly F, Cl, Br and I), carbonate, bicarbonate, hydroxide, oxide, peroxide, nitrite, sulfide, bisulfate, persulfate, glycerophosphate, hypophosphate, borate and titanate. Examples of potentially suitable organic anions include carboxylic acids, alkoxylates, amino acids, peptides, saturated and unsaturated organic acids, and saturated and unsaturated fatty acids. Particular examples include citrate, oxalate, acetate, gluconate, lactate, tartrate, maleate, benzoate, propionate, salicylate, ascorbate, formate, succinate, folinate, aspartate, phthalate, oleate, palmitate, stearate, lauryl sulfate, lanolate, myristate, behenate, caseinate, cylclamate, pantothenate, EDTA and other polyaminopolycarboxylates, saccharin, thioglycolate, laurate, methylparaben, propylparaben, ricinoleate and sorbate anions. Preferably, the ionizing anionic species comprises an acidic anion – *e.g.*, chloride, nitrate, sulfate, acetate, gluconate or oxalate anion.

In a further exemplary embodiment, the concentration of calcium cation is about 0.18% to about 53% by weight in one embodiment. In another embodiment, the concentration of calcium cation is about 0.88% to about 35.2% by weight. In yet another embodiment, the concentration of calcium cation is about 01.8% to about 17.6% by weight. In still another embodiment, the concentration of calcium cation is about 4.4% to about 8.8% by weight. *See* presently pending claims 1-5.

The 35 U.S.C. §102(e) Rejection

Claims 1-3, 12, and 22 stand rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Ito et al. (U.S. Patent No. 5,709,849). This rejection is respectfully traversed.

Ito et al. discloses a cosmetic composition purportedly having suppressed stickiness associated with water-soluble polyhydric alcohols and/or lecithins therein. The compositions include a bivalent metal salt of organic acid. (*See* Col. 1, lines 28-35) The amount of the bivalent metal salt of the organic acid is preferably 0.001% by weight to 5% by weight, more preferably 0.003% by weight to 3% by weight, in the total amount of the cosmetic composition. (*See* Col. 2, lines 35-38)

The Examiner notes that Ito et al. disclose cosmetic compositions of lactic acid and 0.5% calcium chloride, referring to Table 1 of Ito et al. Exemplified therein are compositions containing 2.0% by weight lactic acid and 0.5% by weight calcium chloride, based on total weight of the composition. (*See* Example 1 and Comparative Example 1) Further exemplified by Ito et al. are compositions containing 0.2% by weight lactic acid and 0.05% by weight calcium chloride. (*See* Example 3)

Notably absent from Ito et al. is any discussion of skin irritation. This is not surprising, given that the disclosure of Ito et al. is directed toward compositions imparting high moisture retention, but with the stated improvement of reduced stickiness. Compositions described by Ito et al., irrespective of whether they contain a component that could present skin irritation, certainly do not contain an irritant ingredient in an amount capable of inducing skin irritation, as recited in the presently rejected claims. Indeed, as noted on page 30, lines 23-26, of the application, lactic acid skin-irritant compositions of the present invention, when formulated in an appropriate vehicle, resulted in irritant compositions that contained 7.5% lactic acid. The amount of lactic acid in the cited compositions of Ito et al. – 2.0% by weight and 0.2% by weight – is much less than what Applicants found to be an amount capable of inducing skin irritation according to an exemplary composition of the invention. Ito et al do not teach each and every element of the claimed invention. For this reason alone, withdrawal of this rejection is respectfully requested.

Further, Applicants note that calcium chloride ($CaCl_2$) contains three components – one calcium cation and two chloride anions. The molecular weight of each cation and anion is 40.08 grams and 35.45 grams respectively. Thus, the weight percentage of calcium cation within calcium chloride is 36.11% (40.08 grams / [40.08 grams + 2*(35.45 grams)]). Yet, Ito et al. do not disclose calcium metal salts of organic acids in an amount greater than 0.5% by weight, which equates to calcium cation amounts of up to 0.18% at most. Given the overall nature of the compositions disclosed by Ito et al., it is believed that even if an irritant ingredient in an amount capable of inducing skin irritation was present, an anti-irritant amount of aqueous-soluble divalent calcium cation is certainly not also be present. Again, Ito et al. do not teach each and every element of the claimed invention. For this further reason, withdrawal of this rejection is respectfully requested.

In addition, claim 3 recites a composition "comprising calcium cation in a concentration of from about 0.88% to about 35.2% by weight." In rejecting this claim 3, the Examiner remarks that Ito et al. teaches a composition comprising 0.5% calcium chloride. The combined weight of calcium cation and chloride anion of calcium chloride is well below the lowest amount of calcium cation alone recited in claim 3. The maximum amount of calcium cation potentially present in such compositions is even less – about 0.18%. Thus, calcium cation as recited in claim 3 is clearly not present in such compositions of Ito et al. for this additional reason. Thus, withdrawal of this rejection with respect to claim 3 is independently requested.

Still further, claim 22 recites a composition "wherein said irritant ingredient comprises one or more of the group consisting of 1-pyrrolidone-5-carboxylic acid, capryloyl salicylic acid, α-hydroxy decanoic acid, α-hydroxy octanoic acid, gluconolactone, methoxypropyl gluconamide, oxalic acid, malic acid, tartaric acid, mandelic acid, benzylic acid, gluconic acid, pyruvic acid and phenol." Although the Examiner argues that Ito et al. teaches an irritant ingredient by virtue of its inclusion of lactic acid, Ito et al. certainly do not disclose irritant ingredients recited in claim 22, which are present in composition of the invention in an amount capable of inducing skin

irritation. Thus, withdrawal of this rejection with respect to claim 22 is independently requested.

The 35 U.S.C. §103(a) Rejection

Claims 1-18, 21-25, 52, 55, 57-58, and 61 stand rejected under 35 U.S.C. §103(e) as allegedly being obvious over Mishima et al. (U.S. Patent No. 5,262,153) in view of Ito et al. (U.S. Patent No. 5,709,849), Giddey et al. (U.S. Patent No. 5,053,219), Cook et al. (U.S. Patent No. 2,719,811), and Henderson (U.S. Patent No. 5,296,476). This rejection is respectfully traversed.

As an initial matter, Applicants note that claim 52 was canceled by way of Applicant's Response dated April 4, 2003. Thus, withdrawal of this rejection with respect to claim 52 is respectfully requested due to the claim's prior cancellation.

The Examiner combines a total of five (5) independent documents in rejecting the remaining claims under 35 U.S.C. §103(e). Nevertheless, the Examiner has not established a prima facie case of obviousness in rejecting any of the pending claims. According to Manual of Patent Examining Procedure (MPEP) §2143:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The present rejection does not meet this requirement.

First, there is no suggestion or motivation to combine the reference teachings as the Examiner suggests. The Examiner merely asserts that "[t]he ultimate utility for the claimed combination of organic acid and calcium is old and well known rendering the claimed subject matter obvious to the skilled artisan." No reference is made to any of the five documents for this assertion. This is not surprising, given that none of the five documents discuss the problem or solution afforded by the present invention – obtainment of a composition comprising both an irritant ingredient in an amount capable of inducing skin irritation and an anti-irritant amount of aqueous-soluble divalent calcium

cation and at least one aqueous-ionizable counter-anionic species. Further, no mention is even made of Giddey et al.'s relevance, let alone a motivation or suggestion to combine Giddey et al. with the other four documents cited in this rejection.

Even if there was such a suggestion or motivation to combine the reference teachings to arrive at the present invention, the Examiner has not proven that there would be a reasonable expectation of success. In fact, the Examiner admits that even if the ultimate utility is set forth in the prior art, it is "distanced by various functional limitation[s]." Indeed, the primary reference Mishima et al. is directed to skin-whitening agents, as opposed to the various stated purposes for the compositions of the secondary references. Ito et al. is directed to high moisture retention compositions with suppressed stickiness. Giddey et al. is directed to cosmetic products containing milk constituents. Cook et al. is directed to accelerating oxygen uptake of cells. Henderson is primarily directed to compositions for treating acne. The Examiner has put forth no reasoning or evidence that the asserted combination would reasonably be expected to succeed, which is even more questionable since the secondary references are directed to diverse applications – applications that have substantially different effects than that described by Mishima et al. The stated purpose for the compositions of Mishima et al. is skin whitening.

Furthermore, even if combined as suggested, the Examiner has not established that the asserted combination teaches or suggests all of the claim elements. The asserted combination of Mishima et al. with the secondary references does not overcome Mishima et al.'s deficiencies. The Examiner's currently cited primary document, Mishima et al., was discussed by Applicants in the description of the invention. See page 8, lines 1-9, of the application as filed. As discussed therein, Mishima et al. did not recognize any need or ability to reduce irritation effects in the skin-whitening agents described therein. In fact, the formulations described therein were typically "neutralized" or adjusted to a pH of 5.5 prior to screening of skin whitening testing. *See* Experiments 1 and 2 described therein.

As noted by the Examiner, Mishima et al. do not teach each and every element of the claimed invention. Nevertheless, the asserted combination of Mishima et al. with the

four additional secondary references fails to satisfy the minimum Patent Office requirements needed in order to sustain a prima facie case of obviousness. Withdrawal of this rejection is thus requested.

In view of the foregoing, allowance of all pending claims is respectfully requested. If deemed useful in order to further prosecution of this application to allowance, the Examiner is invited to contact the undersigned by telephone, e-mail, facsimile, or written communication.

Respectfully Submitted,

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